P030016/S001
STAAR Surgical Visian Toric Implantable Collamer® Lens

Tieuvi Nguyen, Ph.D.
PMA Team Leader
Division of Ophthalmic and Ear, Nose and Throat Devices
Food and Drug Administration
Office of Device Evaluation

March 14, 2014

FDA Review Team

Tieuvi Nguyen, Ph.D.	Team Leader
Gene Hilmantel, O.D., M.S.	Clinical
Maryam Mokhtarzadeh, M.D.	Clinical
Don Calogero, M.S.	Engineering
Joseph Jorgens III	Software Validation
Yao Huang, M.S.	Statistics
Youlin Qi, M.D., M.P.H.	Epidemiology/Literature Search
Stacey Priest	Bioresearch Monitoring
Cesar Perez	Manufacturing (GMP)
Eileen Woo, R.N., B.S.N.	MDR Search

Intraocular Lens Regulation

Intraocular Lenses (IOLs)

- Monofocal IOLs
  - » Intended to treat aphakia (absence of natural lens)
  - » Received by most patients undergoing cataract extraction
    - >3 million cataract surgeries performed per year in US**
- "Premium" IOLs
  - » Intended to provide benefits beyond treating aphakia
    - Multifocal, toric, accommodating, phakic
  - » 13% patients implanted with premium IOLs**
- All IOLs are Class 3 medical devices requiring premarket approval (PMA)

**ASD Reports 2012. wwww.asdreports.com/news.asp?pr_id=275

Phakic IOLs

- Lens implanted into the eye without removing the natural lens
  - » Reduce a person's need for glasses or contact lenses

- 2 currently approved
  - » Ophtec Artisan® Phakic IOL
  - » STAAR Surgical Visian Implantable Collamer® Lens for Myopia (MICL)

Toric IOLs

- Intended to correct cylindrical in addition to spherical error in eyes with astigmatism
  - » Astigmatism - Optical defect in which refractive power is not the same in all meridians
  - » Treatment options:
    - Eyeglasses
    - Contact Lenses
    - Laser refractive surgery
    - IOLs
- 4 currently approved
  - Bausch + Lomb Trulign™ Toric Posterior IOL
  - STAAR Surgical UV Absorbing Silicone Posterior IOL
  - Alcon ACRYSOF® Toric IOL
  - AMO TECNIS® Toric 1-Piece IOL

Ophthalmic Standards

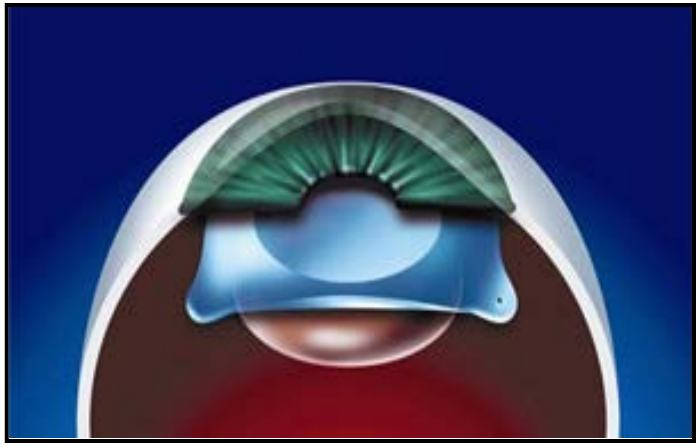
- FDA is working with the American National Standards Institute (ANSI) and the International Standards Organization (ISO) since the 1980's
- FDA Recognized Standards
  - » A consensus standard that FDA has evaluated and recognized for use in satisfying a regulatory requirement and for which FDA has published a notice in the Federal Register (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm)
  - » 36 recognized ophthalmic standards

Toric IOL Standards

- ANSI Z80.30-2010 - Awaiting recognition
- ISO Draft 11979-7 – Being revised to add toric IOLs

Device Description
Visian Toric Implantable Collamer® Lens (TICL)

- Phakic intraocular lens (IOL)
  - » Placed directly behind the iris and in front of the anterior capsule of the crystalline lens
- Toric surface on the anterior side of the optic (major difference between MICL)
- Single piece plate haptic
- Collamer® material
- Convex/Concave optical zone that incorporates a forward vault



http://www.visianiclcommunity.com/home/why-visian-icl/

Device Description

- Visian TICL Calculator Software
  - » Recommends an appropriate lens for the patient
  - » Calculator inputs:
    - Preoperative keratometry
    - Manifest refraction
    - Anterior chamber depth (ACD)
    - Corneal thickness
  - » Calculator outputs:
    - Cylinder powers
    - Range of sphere powers

Proposed Indications for Use

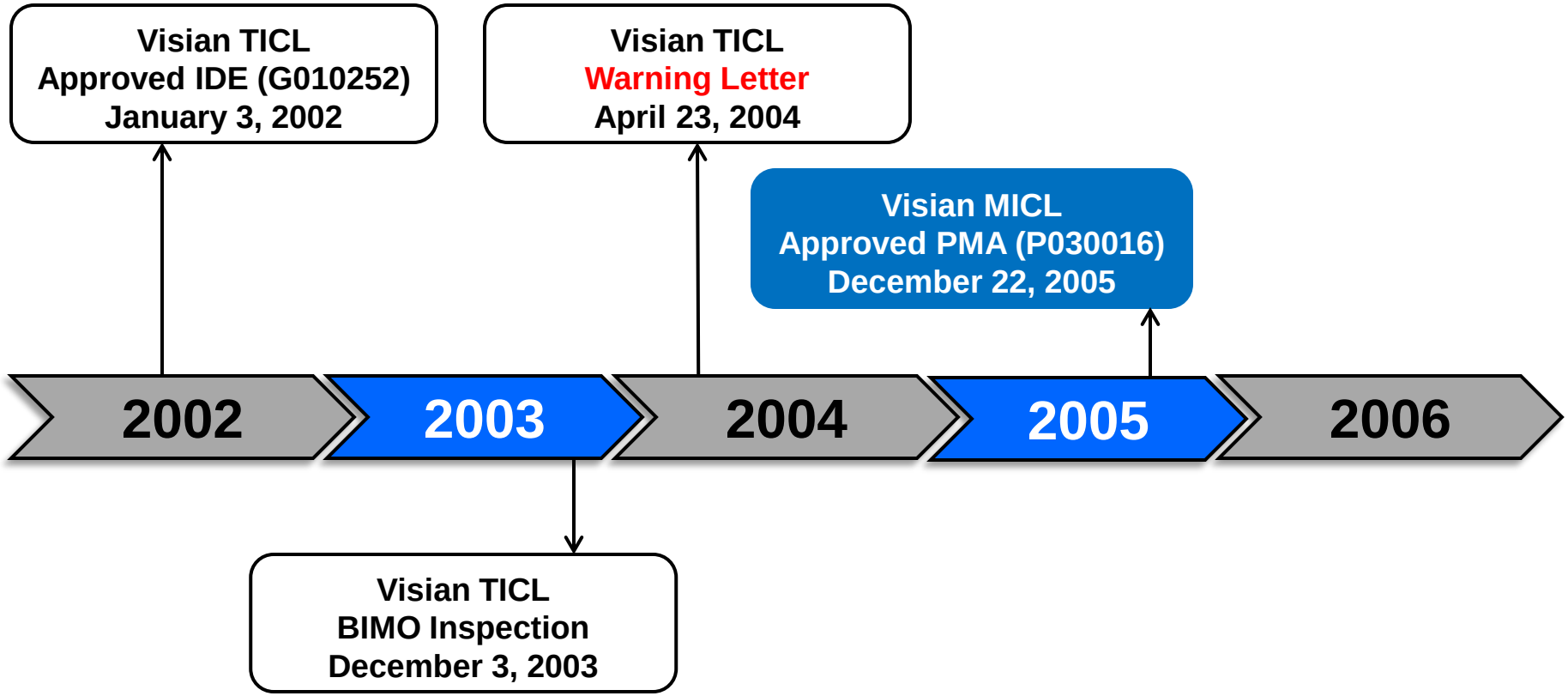
The Visian TICL is indicated for use in adults 21-45 years of age

1. for the correction of myopic astigmatism in adults with spherical equivalent ranging from -3.0D to ≤ -15.0D with cylinder of 1.0D to 4.0D
2. for the reduction of myopic astigmatism in adults with spherical equivalent ranging from greater than -15.0D to -20.0D with cylinder 1.0D to 4.0D
3. with an anterior chamber depth (ACD) of 3.0 mm or greater, when measured from the corneal endothelium to the anterior surface of the crystalline lens and a stable refractive history (within 0.5 Diopter for 1 year prior to implantation)
4. The Visian TICL is intended for placement in the posterior chamber (ciliary sulcus) of the phakic eye

First of a Kind

- Combination of toric and phakic features
- Currently, there is no approved phakic IOL in the US for the correction of astigmatism

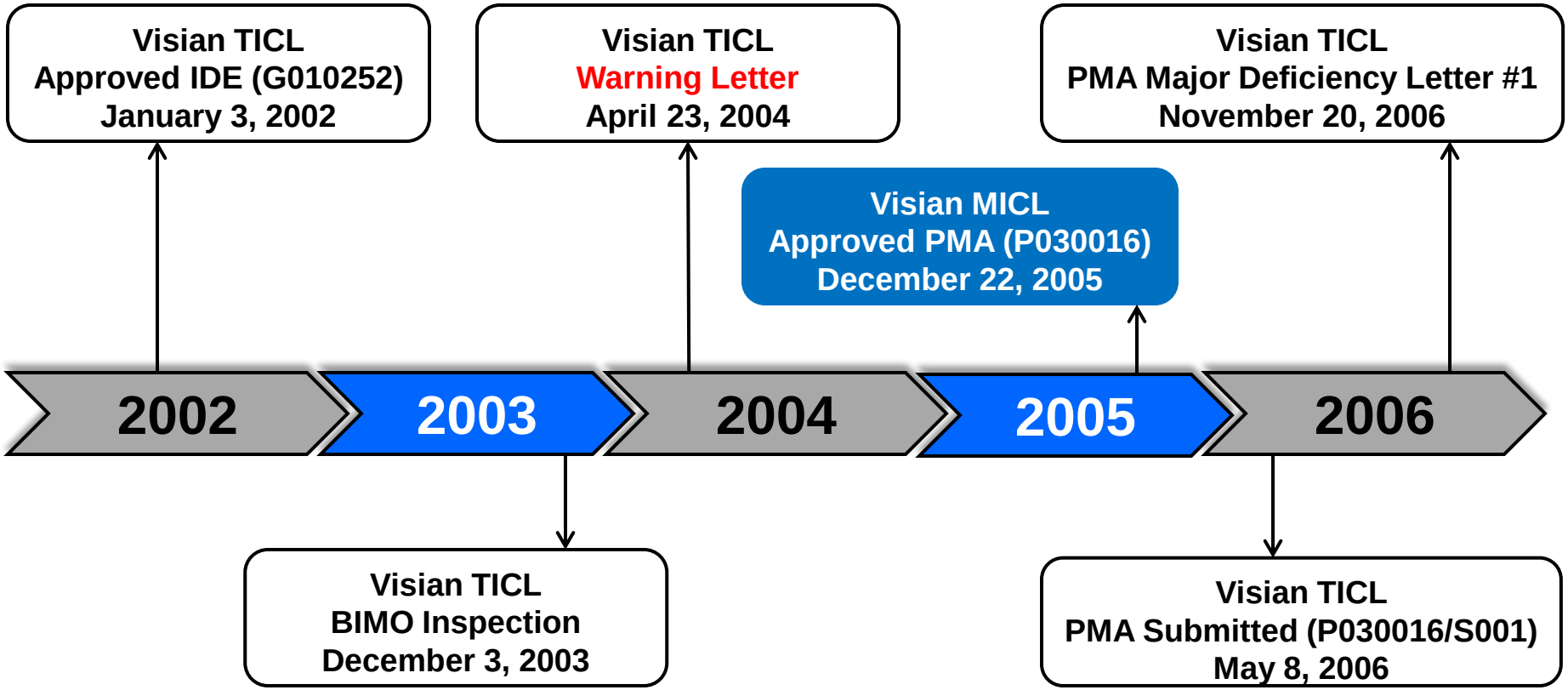
Regulatory History



Warning Letter

- Failure to obtain FDA approval prior to initiating a study
- Failure to ensure continuing Institutional Review Board (IRB) review and approval
- Failure to obtain signed Investigator Agreements from participating investigators
- Failure to provide investigators with adequate information required to perform the study
- May 17, 2004: STAAR provided FDA with their proposed corrective actions to prevent the occurrence of similar violations in current and future studies

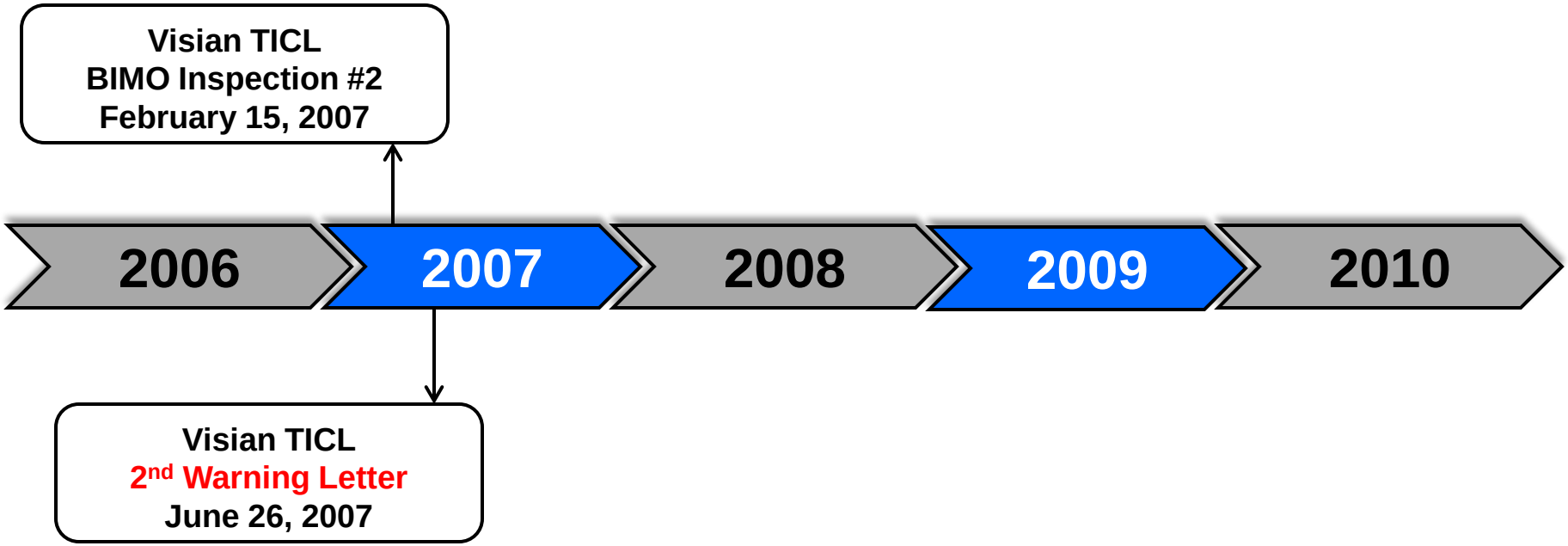
Regulatory History (cont'd)



Major Deficiency – Nov. 20, 2006

- Inadequate analyses to demonstrate the effectiveness of the device for the different cylinder powers
- Uncertainties regarding the labeled TICL power
- Lack of reporting of protocol violations
- Inadequate analysis of subject accountability
- New safety concerns raised as a result of new Medical Device Reports (MDRs) reported at the time for the MICL

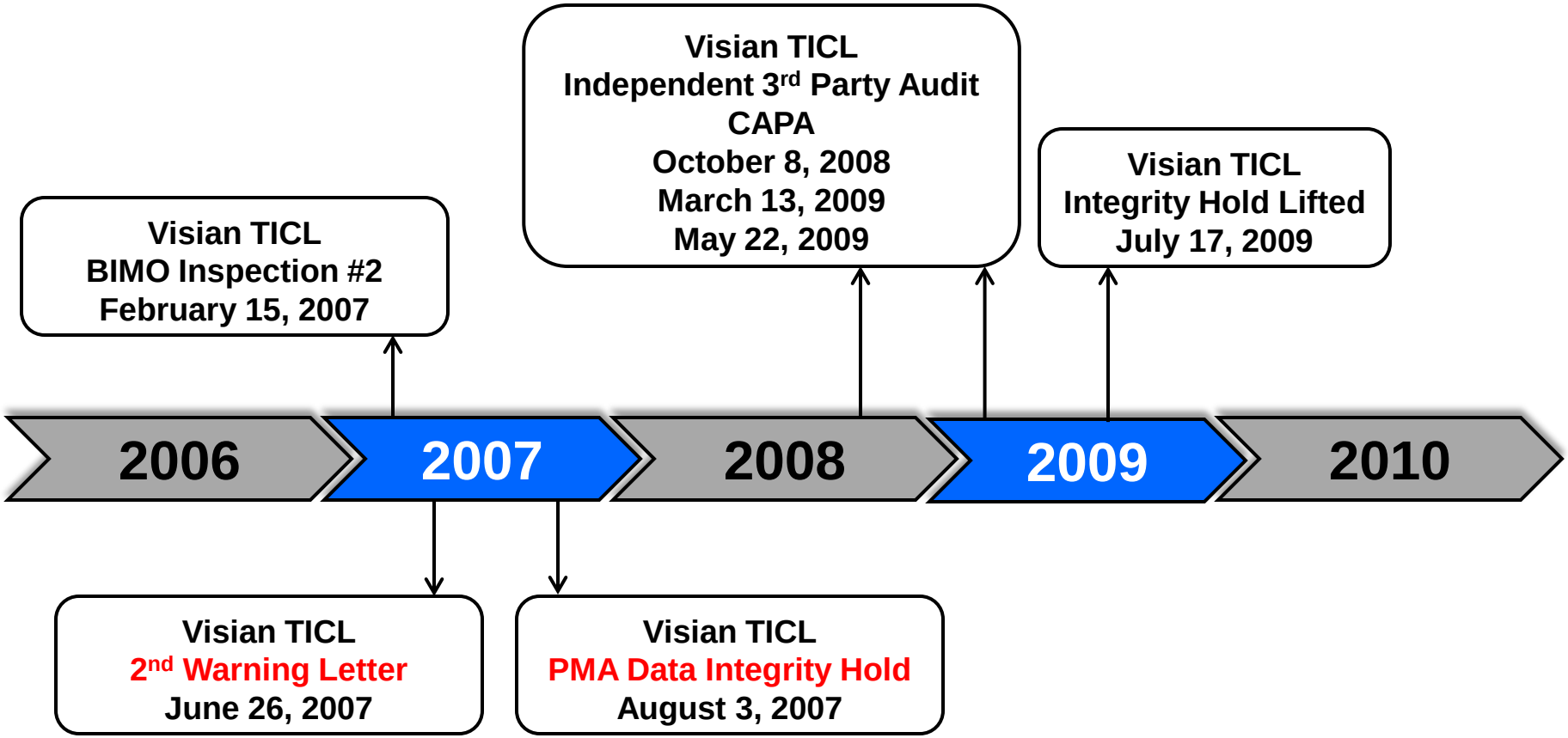
Regulatory History (cont'd)



2ND Warning Letter – June 26, 2007

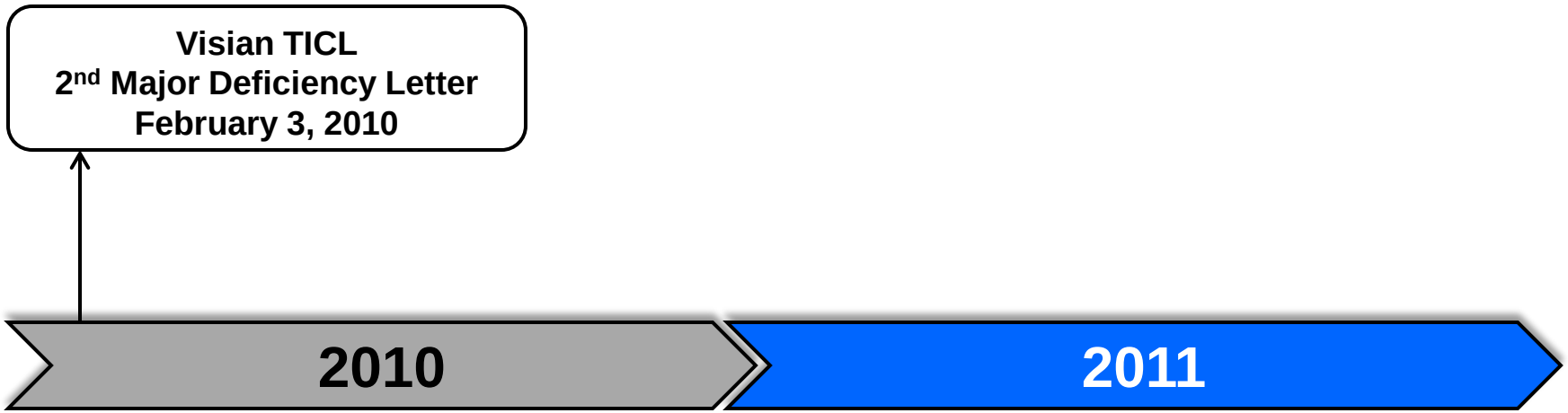
- Failure to submit an IDE study for approval prior to initiation of study
- Failure to Ensure IRB review and approval were obtained
- Failure to ensure investigators' compliance with investigation plan and applicable FDA regulations
- Failure to immediately conduct an evaluation of all unexpected adverse device events
- Failure to submit required reports and information to FDA

Regulatory History (cont'd)



- Independent 3rd party audit – clinical data
- Independent 3rd party system audit
- Corrective and Preventive Action (CAPA)

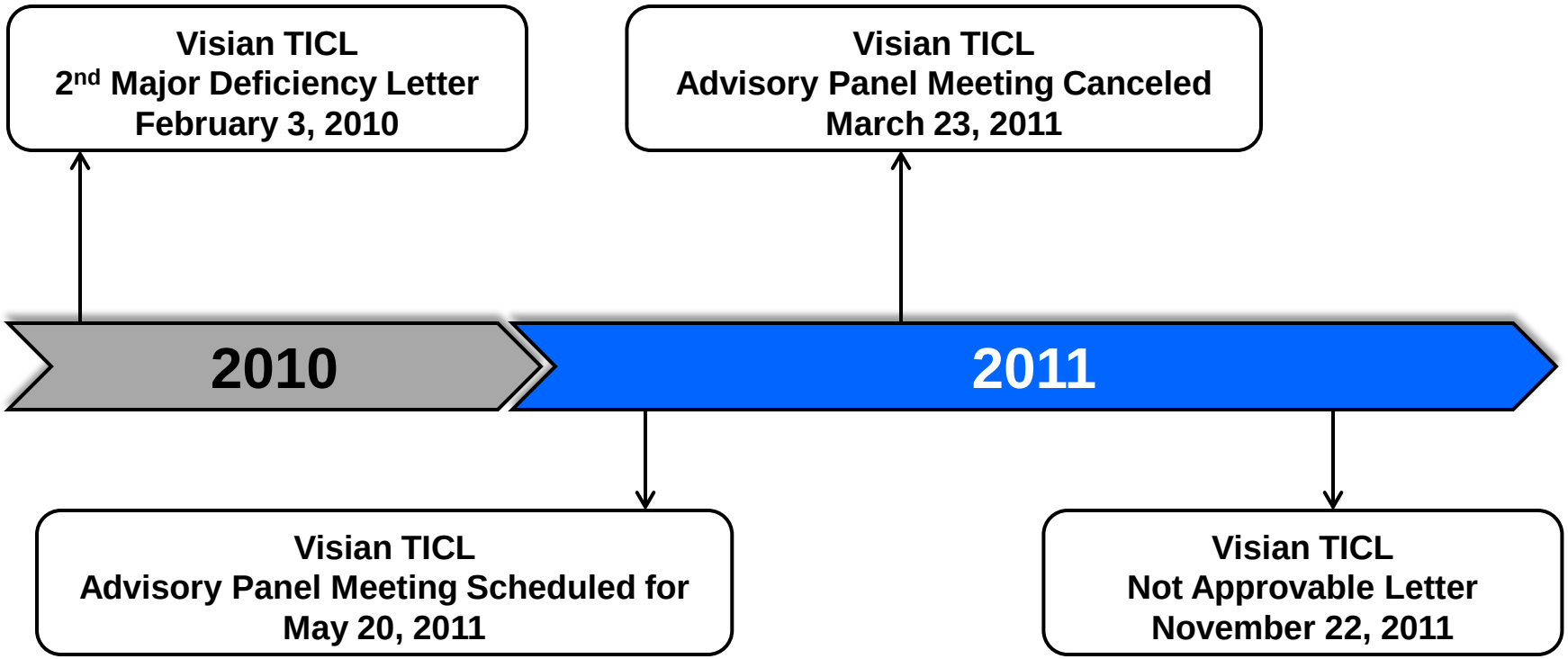
Regulatory History (cont'd)



2nd Major Deficiency Letter - Feb. 3, 2010

- Safety concerns based on endothelial cell loss (ECL) from data obtained from the MICL post-approval study
- Lack of an evaluation of visual distortion for high-astigmatism subjects to support approval of the full range of requested cylinder
- Concerns regarding the analysis of rotational stability

Regulatory History (cont'd)

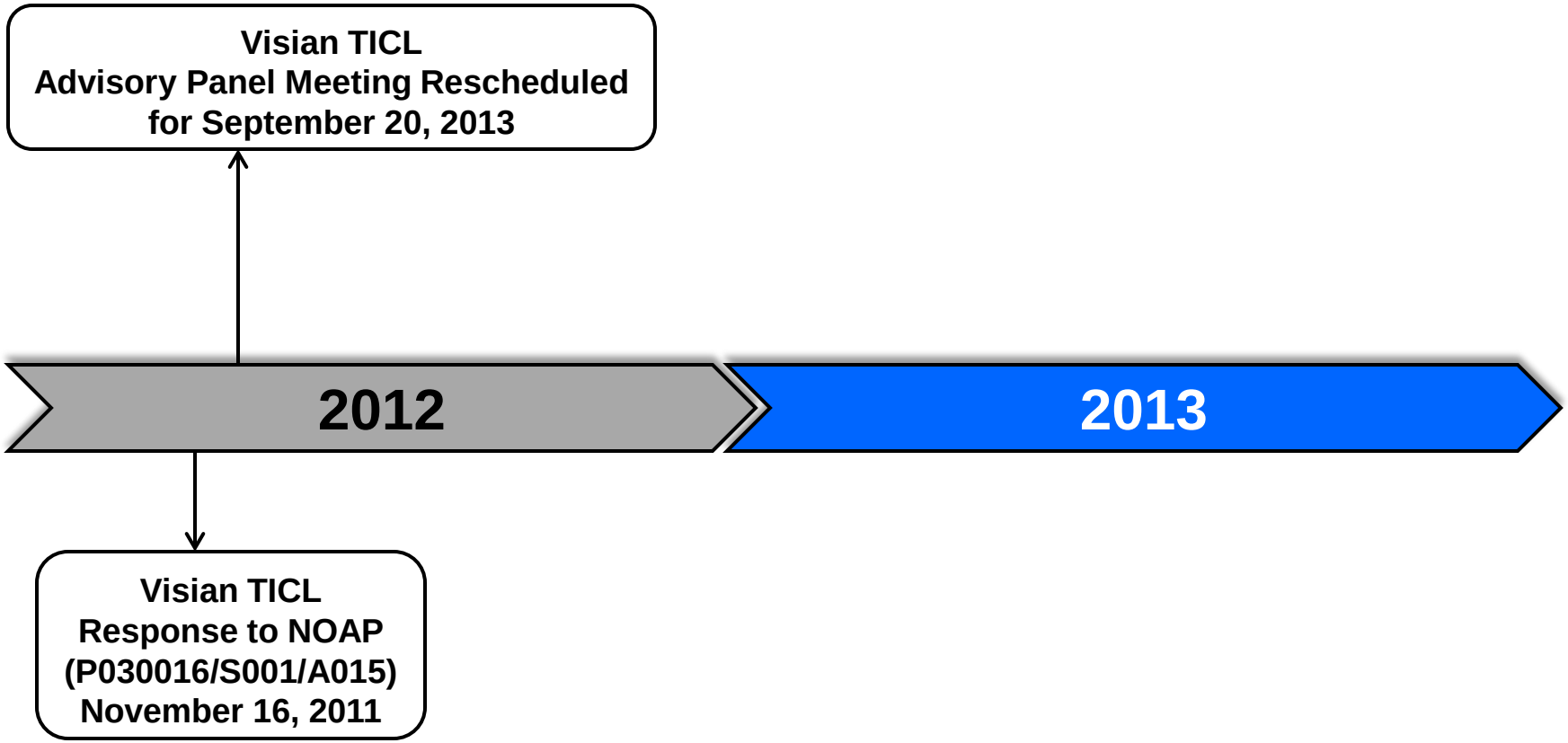


- Contradictory data
- Analyses based on different databases

Not Approvable Letter – Nov. 22, 2011

- Inconsistency of study database
- Low subject accountability
- Large number of protocol deviations
- Lack of adequate software and mechanical validation studies

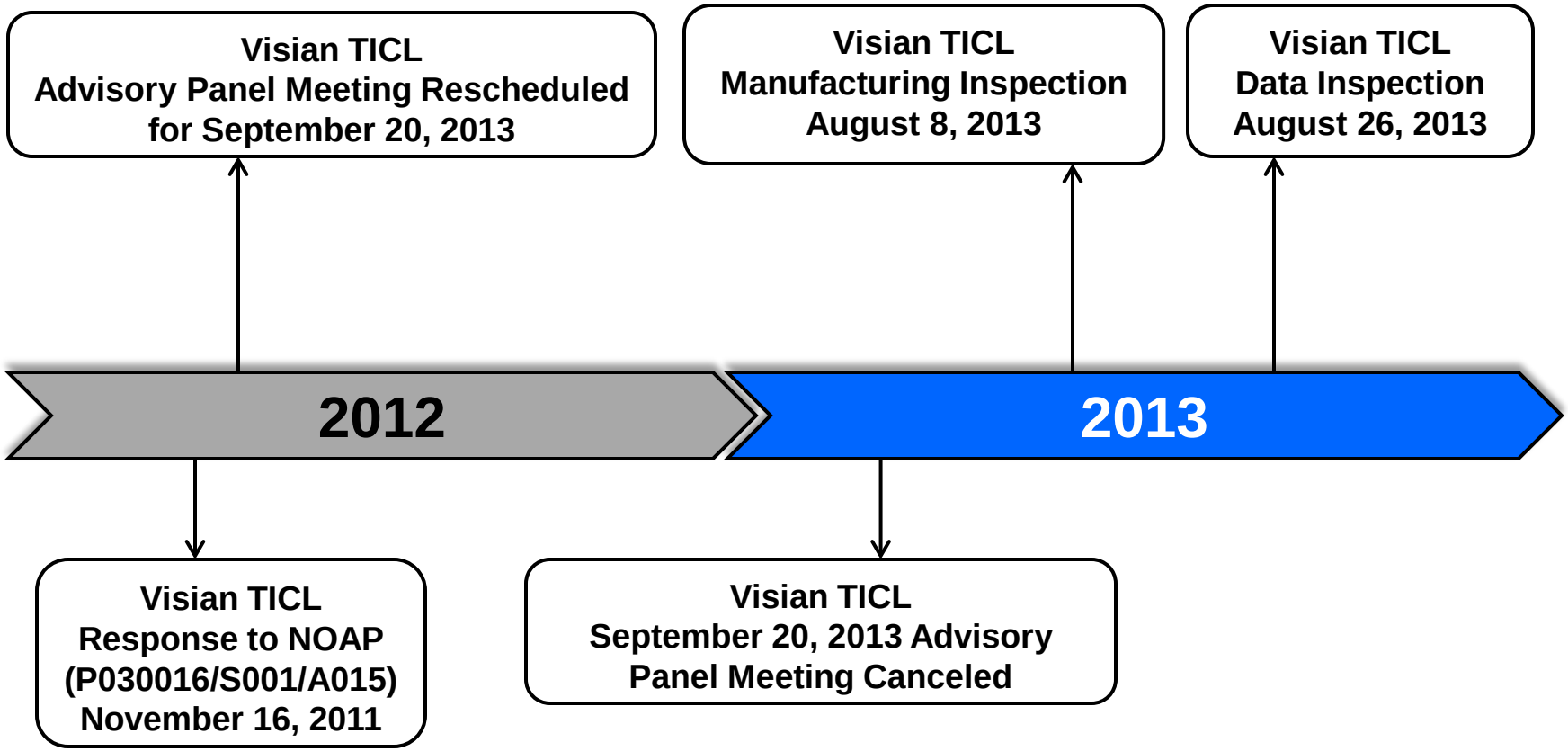
Regulatory History (cont'd)
Current Amendment (2012 – Present)



New Concerns

- Unapproved Design Changes
  - » The design was changed after the initial approval of the IDE study
  - » Unapproved design was implanted in study subjects
- Manufacturing Procedure
  - » Adequacy of quality control processes and test equipment
- Previously unreported protocol deviations

Regulatory History (cont'd)
Current Amendment (2012 – Present)



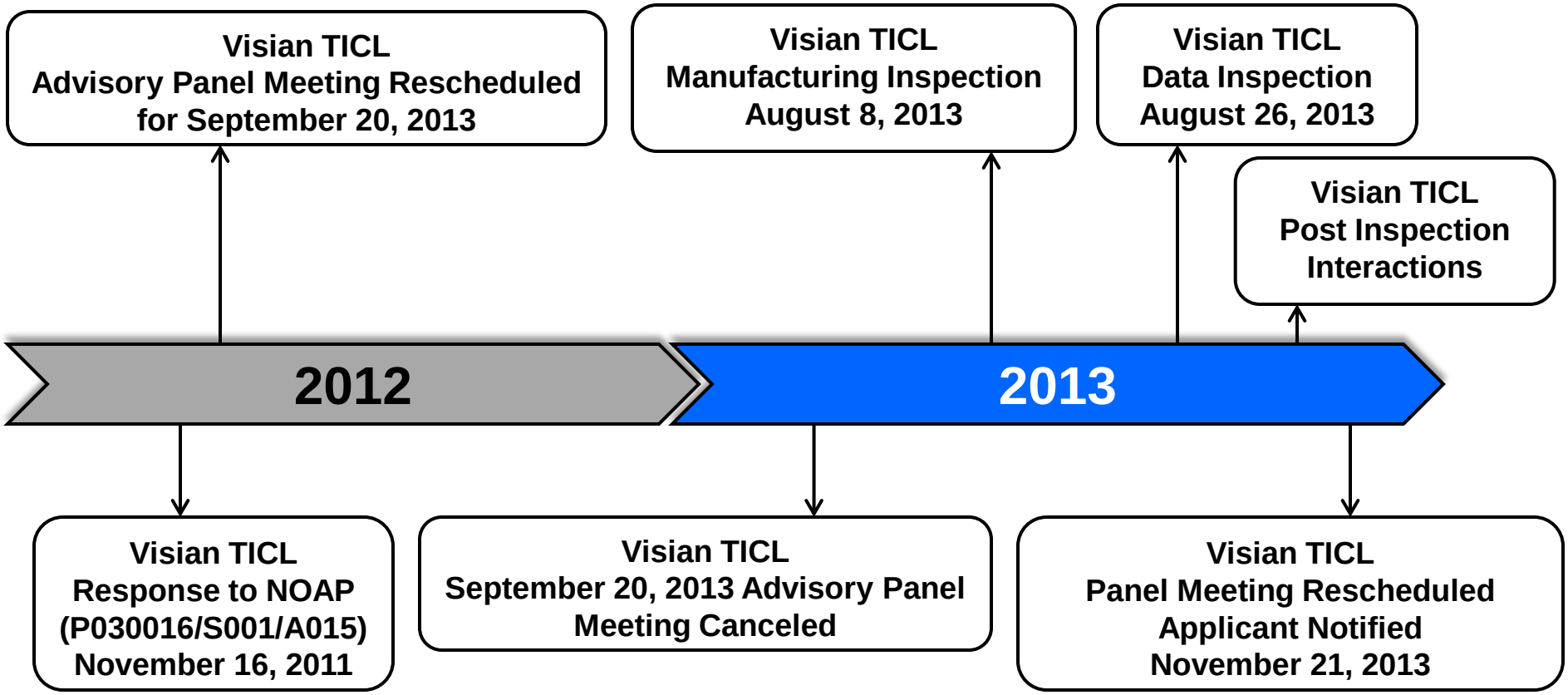
Manufacturing Inspection – Aug. 8, 2013

- Purpose
  - » Verify manufacturing and quality control procedures
  - » Verify manufacturing qualification studies for the TICLs since 2002
  - » Identify which version of the device design each subject in the clinical trial received
- Resulted in three inspectional observations
  - » Device master record not adequately maintained
  - » Procedures for CAPA have not been adequately established
  - » Inadequate procedures to nonconforming product

Data Inspection – Aug. 26, 2013

- Purpose
  - » Investigate the conduct of the clinical study
  - » Determine process used to determine protocol deviations
  - » Evaluate reporting of protocol deviations after the third party audit
  - » Determine source of new protocol deviations
- Post-Inspection Discussion Items
  - » Failed to validate investigational lens software
  - » Failed to amend protocol to specify ETDRS
  - » Inability to provide evidence of adequate training

Regulatory History (Cont'd)
Current Amendment (2012 – Present)



Rationale for Today's Meeting

- To solicit Panel's opinion on:
  - » Safety and effectiveness of this first of a kind phakic toric lens

- FDA's Presentation:
  - » Safety – Maryam Mokhtarzadeh, M.D.
  - » Effectiveness – Gene Hilmantel, O.D., M.S.
  - » Post Approval Study (PAS) – Youlin Qi, M.D., M.P.H.

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STAAR Surgical
Visian Toric Implantable Collamer® Lens

Maryam Mokhtarzadeh, M.D.

Medical Officer

Division of Ophthalmic and Ear, Nose and Throat Devices

Food and Drug Administration

Office of Device Evaluation

March 14, 2014

Available Clinical Data

- MICL PMA
- MICL Post-Approval Studies (PAS)
- Medical Device Reporting (MDR) System Analysis
- Literature Review (MICLs and TICLs)
- TICL PMA

MICL PMA

- Prospective, nonrandomized, multicenter, single arm study
- Control = Preoperative state of treated eye
- 526 eyes of 294 subjects
  - » 470 followed for 1 year, 369 followed for 3 years
- Key enrollment criteria
  - » Must be between 21 and 45 years of age
  - » Must have moderate to high myopia
    - -3.0 D to -20.0 D measured as manifest refraction spherical equivalent (MRSE)
    - Cylinder ≤ 2.5 D

Full Summary of Safety and Effectiveness Data (SSED):
http://www.accessdata.fda.gov/cdrh_docs/pdf3/P030016b.pdf

MICL PAS Studies

- **PAS #1 – Continued Follow-Up of PMA Cohort**
  - » To continue data collection on AE and ECD
  - » Of 526 eyes implanted in IDE study, final ≥5 yr data for 335 eyes
  - » Completed; labeling revisions pending
- **PAS #2 – New Enrollment Adverse Events**
  - » To estimate incidence of MICL AEs/complications postmarket
  - » Multi-site prospective registry
  - » 3,000 eyes enrolled (expect 2,000 eyes with 5 yr data)
  - » Ongoing
    - Final study report expected on December 31, 2018.
- **PAS #3 – Axial Length Study**
  - » To assess whether ICL changes measurement of axial length
  - » Completed, MICL labeling updated to reflect study results

Medical Device Reporting Analysis

Division of Surveillance – Office of Surveillance and Biometrics

- Nationwide passive surveillance system
- Manufacturer and User Facility Device Experience (MAUDE) Database
  - » Mandatory (Manufacturers and importers; User facilities)
  - » Voluntary reporting (MedWatch) (Healthcare providers; Consumers)
- Limitations:
  - » Under-reporting, Data quality issues, Inability to determine rate, Biased information, Inability to determine causality
- MDR MAUDE Search:
  - » Brand Name: “Visian” “ICL” & “Implantable Collamer Lens”
  - » Date Entered: from Dec 22, 2005 to May 1, 2013
  - » Results: 3,225 reports

Literature Review

Division of Epidemiology - Office of Surveillance and Biometrics

- Systematic literature review of the safety profile of the MICL and TICL
- Databases: EMBASE and MEDLINE
- Search Terms**:** 'staar' OR 'visian' OR 'phakic icl' OR 'phakic implantable' OR 'phakic implantable collamer lens' OR 'implantable collamer' OR 'implantable contact lens'
- 455 citations identified
  - » Narrowed to 43 articles from January, 2006 to May 2013

TICL Study Design

- Prospective, Non-Randomized, Unmasked, Single arm, Multicenter (7 sites)
- Preoperative status used as a control
- Monocular or Binocular Implantation
- Follow-up 1 year
- Study IOL: Visian TICL
  - » Calculator used to determine cylinder power (ranging from +1.5 D to +6 D in saline)
- Control IOL: None

TICL Study Design: Safety

- MICL data intended to be used for key safety evidence
- Safety Parameters:
  - » Preservation of Best Spectacle Corrected Visual Acuity (BSCVA)
  - » Slit Lamp Examination (SLE) Results
  - » Intraocular Pressure (IOP)
  - » Incidence of Complications and Adverse Events (AE)
- "Target outcomes that define success"(Protocol):
  - » Maintenance of Best Spectacle-Corrected Visual Acuity (BSCVA)
    - < 5% of eyes should lose 2 lines or more BSCVA
    - ≤ l% of eyes should have BSCVA worse than 20/40, if 20/20 or better BSCVA preoperatively

Visual Disturbance Assessment: TICL Study vs. ANSI Recommendations

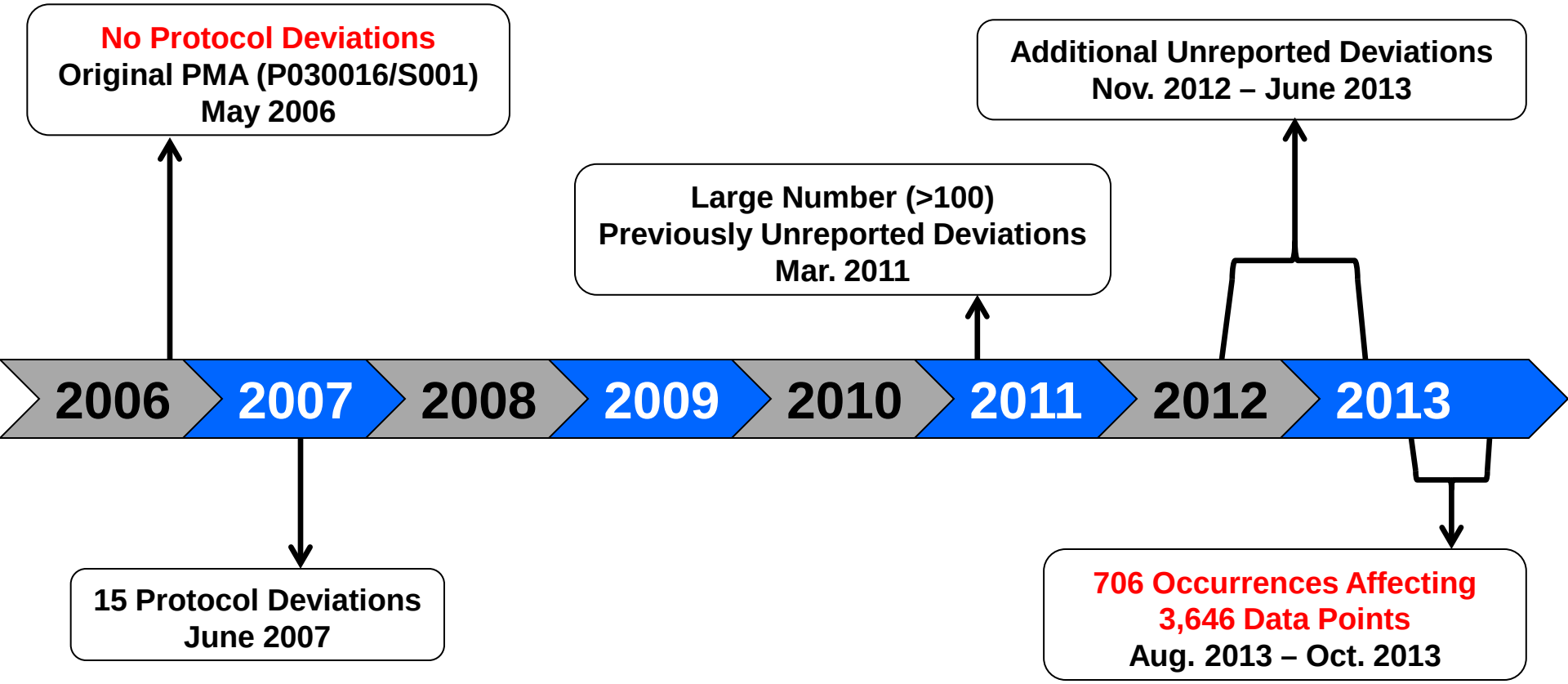
TICL Study	ANSI Z80.30 2010 Recommendations for Toric Phakic IOL (modification of approved IOL)
• Non-validated questionnaire	• Validated questionnaire
• No spatial distortion questions	• Add spatial distortion questions

Patient-Reported Outcome Measures Labeling Guidance (2009):
http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

TICL Study: Demographics

- 210 eyes from 124 subjects
  - » 55.6% Female (69/124)
  - » 82.3% Caucasian (102/124)
  - » Mean age (± standard deviation) at implantation:
    - 35.0 ± 6.8 years (range 21 to 45 yrs old)
  - » Mean preoperative manifest refraction spherical equivalent (MRSE):
    - -9.37D ± 2.67 (range -19.50D to -2.38D)
  - » Mean preoperative manifest refractive cylinder:
    - 1.95D ± 0.84 (range 1.00D to 4.00D)

TICL Study: Evolution of Protocol Deviation Reports



TICL Study:
Protocol Deviations as of 12/20/2013

	Type of Deviation	"Occurrences"	"Data Points"	Eyes
	Total	**706**	**3,646**	**210**
"MAJOR"	Lens power outside protocol approved range	32	32	32
	Lens length not selected according to protocol	18	18	18
	Noncompliance with surgical procedure	4	4	4
"MINOR"	Unapproved randomization (i.e. unapproved protocol)	41	41	41
	Eyes outside of the inclusion criteria	3	3	3
	Inconsistency between protocol and CRF	13	2730	210
	Non-compliance with pre-surgical procedures	8	8	8
	Out-of-window visits	123	123	88
	Missed visits	33	33	25
	Missing information	272	495	
	Manufactured axis not according to protocol	126	126	126
	Snellen instead of ETDRS	33	33	18

Missing Data

Type of Deviation	Occurrences	Data Points	Eyes
Missing Information	272	495	At least 93
Observed lens orientation	213	213	93
Failure to implement Subjective Patient Evaluations	24	216	22
Manifest Refraction or Visual Acuity	18	18	6
IOP	4	4	4
Missed Subjective Patient Evaluation questions	4	4	4
LOCS Score	3	15	3
Complication/Adverse Event	5	5	3
Form 4 incomplete Eye #149	1	20	1

Excessive missing data can introduce an unacceptable level of uncertainty in the results and invalidate the study conclusions

TICL Study: Error in Power and Diameter Measurements

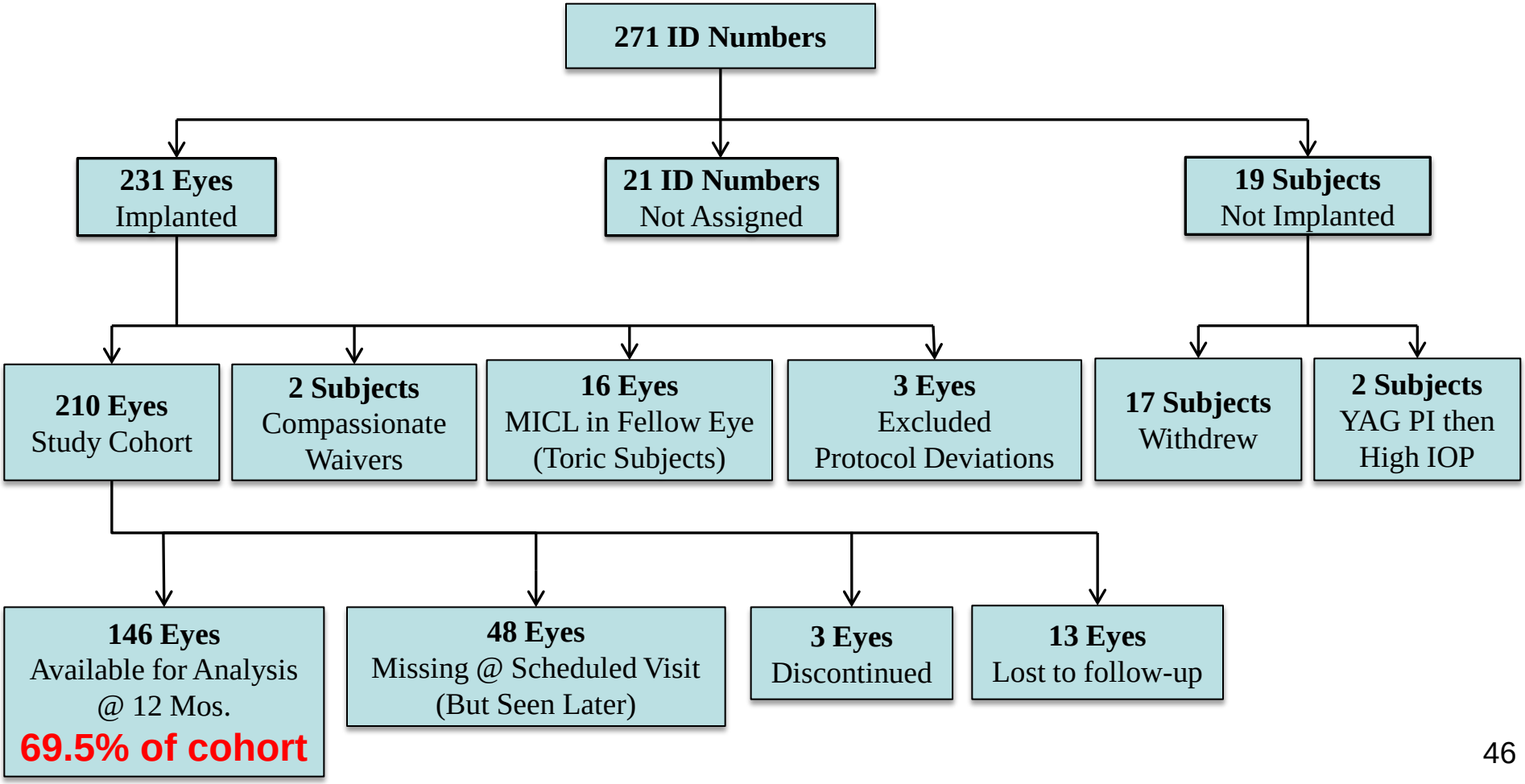
- ISO 11979-1: Defines labeled IOL power as the power of the lens in aqueous humor at 35°C
- TICLs in IDE study mislabeled with incorrect in-situ power and diameter
  - » Labeled measurements from hydration in saline rather than Balanced Salt Solution (BSS)
    - Actual ICL powers implanted lower than labeled by factor of ~ 0.782
    - Actual ICL diameters larger than labeled by ~ 5%
- Conversion issue also occurred in the MICL IDE study
  - » Issue identified by FDA after the MICL Panel Meeting in 2003
  - » Applicant proposed corrective actions, including modifications to labeling and power/size selection software
    - FDA accepted these corrective actions

TICL Study: Device

Device Parameters		Protocol Approved	Studied	Proposed for Approval
Overall Length (mm)	Saline	11.5 to 13.5*	11.5 to 13.5	n/a
	BSS	n/a	12.1 to 14.2	12.1 to 13.7
Spherical Power (D)	Saline	-3.0 to -20.0	-5.5 to -23.0	n/a
	BSS	n/a	-4.3 to -18.0	-3.0 to -16.0**
Cylinder Power (D)	Saline	1.5 to 6.0	1.0 to 6.0	n/a
	BSS	n/a	0.8 to 4.7	1.0 to 4.0
# of Cylinder Correction Axes		4	80	180

* Based on IDE
** Spherical Equivalent

TICL Study:
70.5% Accountability at 1 year



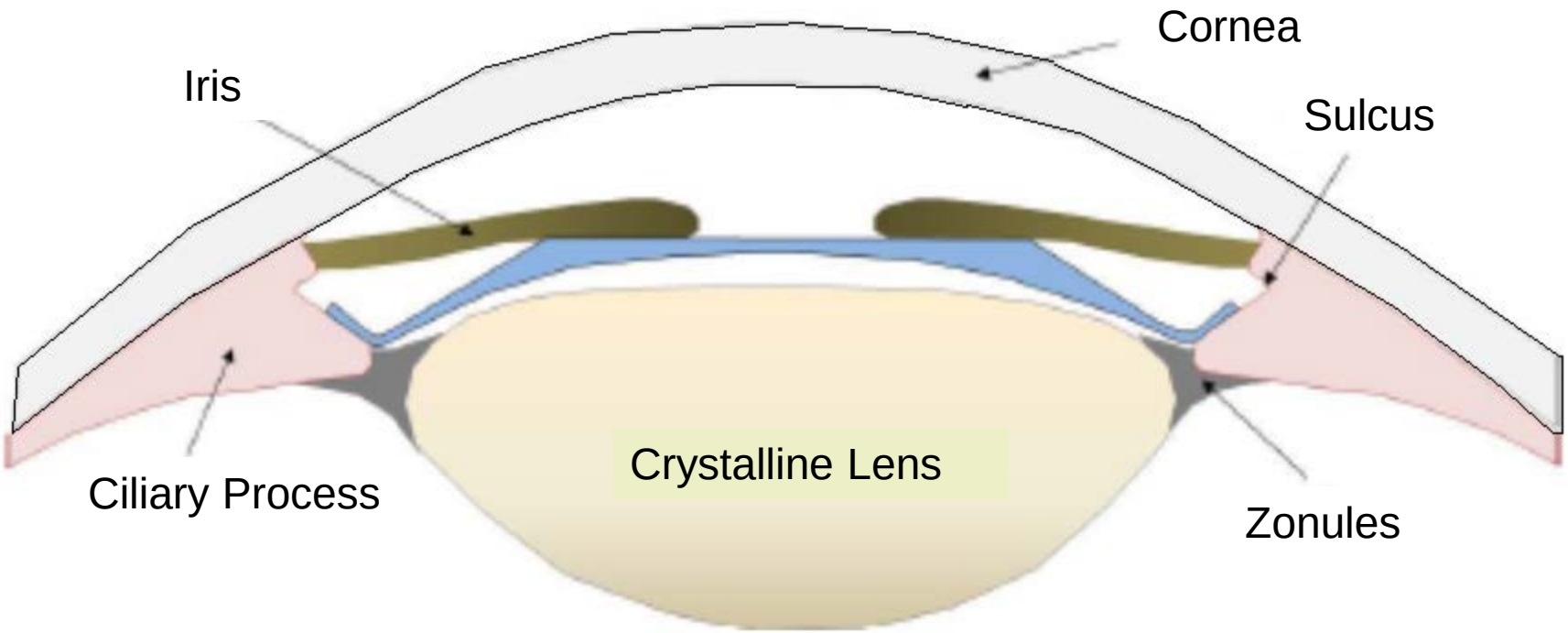
Question for Panel Discussion

In light of the study conduct, including but not limited to:

- 3,646 data points affected by protocol deviations
- Significant amount of missing data
- Within-window accountability of 70.5% at 12 months
- 68% (143/210) of eyes implanted with lenses not according to protocol

Do the data generated from the TICL study represent valid scientific evidence for assessment of device safety and effectiveness?

TICL Study: Safety Results*



* Safety data leveraged from MICL

TICL Study Key Safety Results: Preservation of BSCVA

- 3/194 eyes (1.5%) lost ≥ 2 lines of BSCVA at 12 months postoperatively
  - » Protocol target: < 5% of eyes should lose 2 lines or more BSCVA
- No eyes (0%) had BSCVA worse than 20/40 (if preoperative BSCVA 20/20 or better) between 1 and 12 months postoperative
  - » Protocol target: ≤ l% of eyes should have BSCVA worse than 20/40, if 20/20 or better BSCVA preoperatively
- Persistent loss of BSCVA > 2 lines occurred in one eye (0.5%); loss of 2 lines in 2 eyes (1.0%)

TICL Study Key Safety Results: Adverse Events (All Eyes)

Adverse Event	Cumulative % (n/N)	ISO Safety and Performance Endpoints (SPE)
Endophthalmitis	0% (0/210)	0.1%
Hypopyon	0% (0/210)	0.3%
IOL Dislocation	0% (0/210)	0.1%
Cystoid Macular Edema	0% (0/210)	3.0%
Pupillary Block	0% (0/210)	0.1%
Retinal Detachment	**0.5% (1/210)**	0.3%
Surgical Reintervention	**2.4% (5/210)**	0.8%
Corneal Edema (after 1 week)	0% (0/210)	
Iritis (after 1 week)	0% (0/210)	
Raised IOP Requiring Intervention	**0.5% (1/210)**	

TICL Study Key Safety Results:
Surgical/Perisurgical Complications (Total = 12)

- 7 (3.3%) TICLs removed & reinserted during implantation
- 3 (1.4%) Additional iridotomy
- 1 (0.5%) Aborted TICL procedure*
- 1 (0.5%) Excessive forward vault

** TICL was implanted upside down. During manipulation the TICL was torn and then removed. A new TICL was ordered and implanted 2 weeks later.*

MICL PAS Study #1: Key Safety Results

- Cumulative probability *per eye* at 7+ yrs:
  - » Anterior Subcapsular Opacity (ASO): 5.89% for ≥ trace opacity, 1.52% for clinically significant
  - » Cataract Extraction: 2.09%
  - » Glaucoma: 1.33%
  - » Remove & Replace MICL: 1.71% (unchanged from yr 3)
  - » Retinal Detachment: 0.57% (unchanged from yr 3)
  - » Additional YAG iridotomy: 3.23% (unchanged from yr 1)
  - » Inflammation: cumulative risk not reported,
    - no reports of flare or cellular reaction at ≥1 yr

MDR Findings (Dec 22, 2005 – May 1, 2013)

- Vaulting ---------- 1,590
- Explants/lens removals ---------- 1,556
- Lens replacements/exchange---------- 1,336
- Narrowing of the angle ---------- 472
- Elevated or increased IOP ---------- 451
- Cataract ---------- 298
- Glaucoma ---------- 59
- Corneal edema/decompensation--------- 30

Key Slit Lamp Findings: TICL Study Results

- 6 eyes (2.9%) ASO
  - » 2 cases (1.0%) had clinically significant cataract
  - » 1 TICL explanted at 1 week postop for ASO, though asymptomatic
- Pigmentary deposits on TICLs reported
  - » No reports of TICL opacities, inclusions, glistenings, and/or discolorations

Key Slit Lamp Findings: MICL PMA Results

- ASO observed in 14 eyes (2.7%)
  - » 7 (50% of ASO) observed within 1st postoperative week
  - » 2 (0.4% of the total cohort) ASO progressed to clinically significant
- 5 (1%) clinically significant nuclear cataracts

Key Slit Lamp Findings: MICL PAS Study #1 Results

- Complications at a rate > 2%:
  - » ASO in 31 eyes (5.9%)
    - not all clinically significant
  - » Abnormal pigment in angle, 16/335 eyes (4.8%)
  - » Pigment deposition on IOL, 44/526 eyes (8.37%)
  - » Transillumination defect, 52/526 eyes (9.89%)

Key Slit Lamp Findings: MICL PAS Study #1 Conclusions

- Risk of new cataract:
  - » Per person rate of new clinically significant ASO slowly but consistently increasing over time: ~0.33 % incidence new cases/year over 7 yrs
  - » Reduction of hazard ~30% with each diopter of decrease in negative lens power

Key Slit Lamp Findings: MDRs and Published Literature

- MDR Analysis
  - » 298 MDRs related to cataract
- Published Literature
  - » 18 cohort studies
  - » Incidence of ASC ranges from 0-28%
    - Avg follow-up 39 months (range: 6-120)

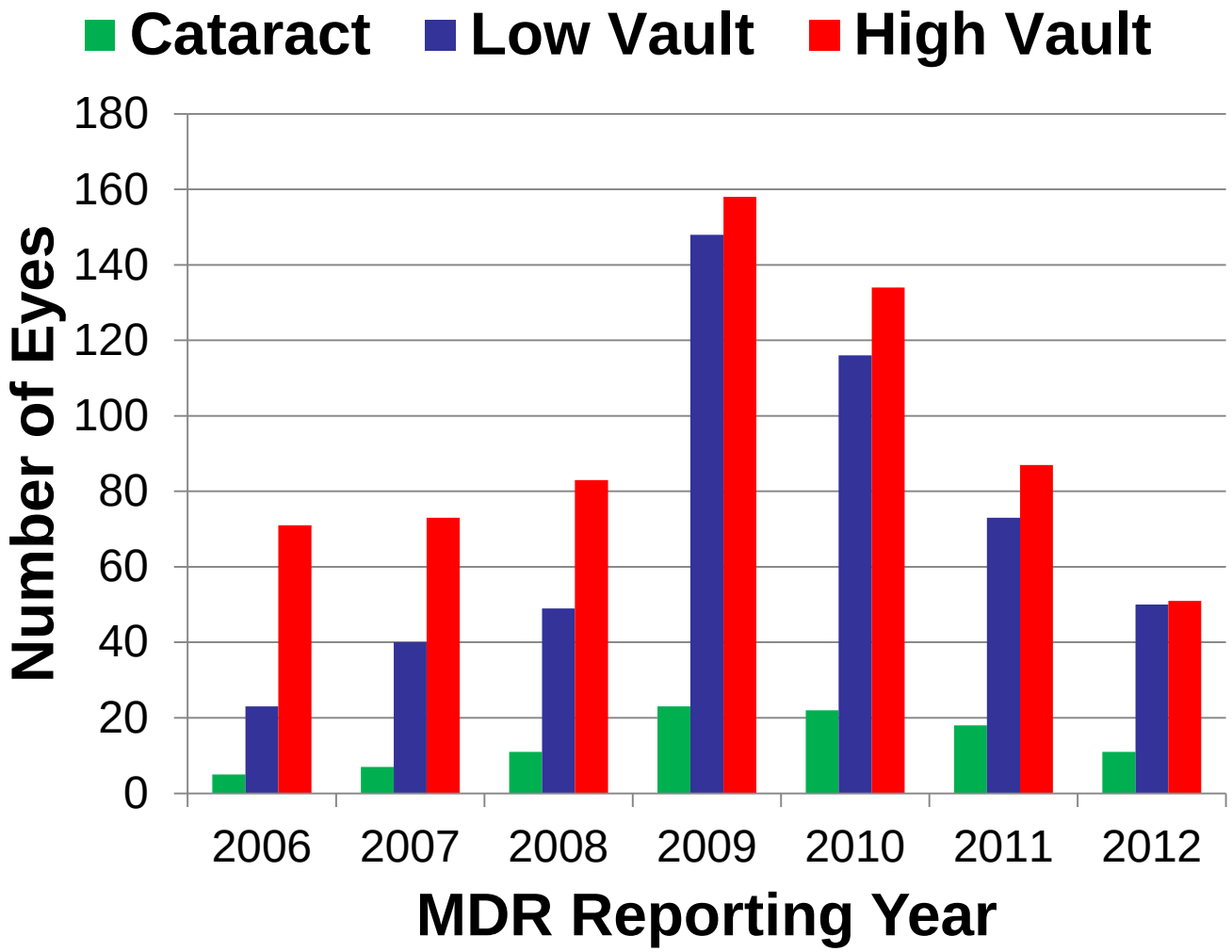
Secondary Surgical Interventions (SSIs): TICL Study

- SSIs reported in 6 eyes (2.9%)
  - » 5 (2.4%) “Visian TICL related surgeries”
    - 3 TICLs removed, (discontinued from study)
      - – 1 excessive vault
      - – 1 asymptomatic ASC
      - – 1 visual disturbance
    - 1 TICL replacement
      - – lens too long, causing excessive vault and iridocorneal touch
    - 1 TICL repositioning (3 days postop)
      - – 25° rotation from the desired position
  - » 1 retinal detachment repair

SSIs: MICL PMA

- 3.1% (16/526) incidence of SSI
  - » 0.6% (3/526) eyes MICL removed
    - MICL too long causing highest vaults
  - » 0.8% (4/526) eyes MICL repositioned
  - » 1.5% (8/526) eyes MICL replaced
  - » 0.2% (1/526) eye MICL replaced then removed
- 3.8% (20/526) Secondary Refractive Procedures
- 0.2% (1/526) Iris Prolapse Repair

MDR Reports – Major Explant Categories



Vault Data: TICL Study

- 89%-97% investigators recorded vault at a given visit
  - » Amount of vault recorded in 182 - 203 eyes
  - » Range: 0%-400% central corneal thickness
    - Form 1, mean = 108%, SD = 66%
    - Form 6, mean = 105%, SD = 56%
  - » Significant within-eye variation across visits
    - Within-eye range: 0%-225% corneal thickness.
    - 48 eyes with maximum reported vault > 150%
    - 44 eyes with minimum reported vault < 50%
    - 44% (92/210) eyes had report of vault outside optimal range

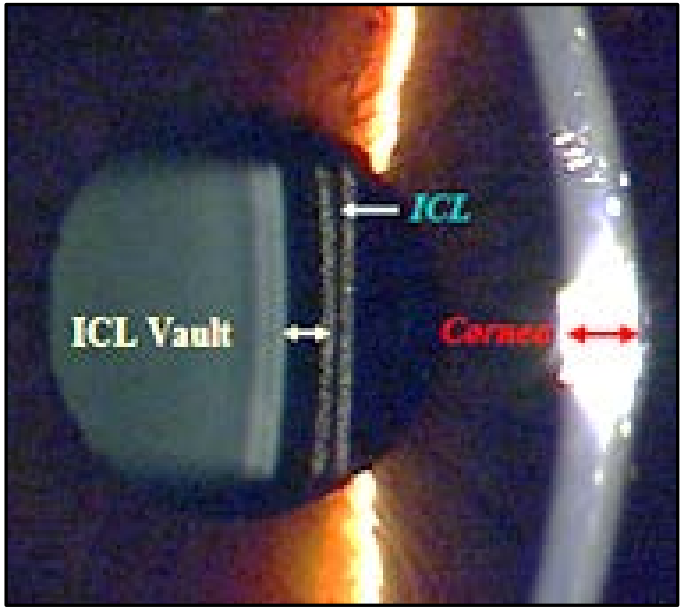
TICL Vault: Proposed Labeling

Postoperative Visian TICL Vault

- Assessed 24 hrs postop
- Optimal vault: 50%-150% central corneal thickness (250-900 microns)
- Asymptomatic vault outside range may not require intervention

Visian TICL Removal

- Recommended:
  - » Insufficient vault & early ASC
- May be necessary:
  - » Narrowing of anterior chamber angle
  - » Other



Question for Panel Discussion

Does the labeling provide adequate instruction regarding evaluation of postoperative lens vault?

Factors Impacting ICL Vault: Literature

- Position of footplates in relation to sulcus and ciliary body
- Orientation of ICL plate haptic major meridian
- Degree of myopia
- Accommodation
- Age
- Lighting
- Time from lens implantation
- Manufacturing of the TICL impacts the clearance
  - » Sagitta value
  - » Power of the posterior surface

ICL Position

TICL Study Protocol:

- "…footplates fit snugly in the sulcus…"

TICL PMA:

- Proposed IFU: "…placement in the posterior chamber (ciliary sulcus)…"
- Communicated to FDA:
  - » "…the footplates... interact with the ridges and grooves on the surface of the ciliary process…"
  - » "In the majority of cases the ends of the footplates remain on the ciliary processes. However in instances where the ends of the footplates come into contact with the sulcus, compression forces may be created. This results in a change in the curvature of the haptic and may increase lens vault."

TICL Sizing

- TICL Protocol:
  - » Collected data on white to white diameter and anterior chamber depth (ACD)
- TICL Study:
  - » Alternate sizing methods used by some investigators, ex. ultrasound biomicroscopy
- Proposed Labeling:
  - » Recommendations made based on white to white diameter and anterior chamber depth (ACD)
  - » Direct measurements of the ciliary sulcus such as ultrasonic biomicroscopy (UBM) should be considered as alternative methods

ICL Sizing in Literature

One article states:

"Another layer of complexity in selecting the Visian pIOL is the discrepancy between the manufacturer's 'optimized' recommendations and the U.S. Food and Drug Administration (FDA) guidelines as presented on the manufacturer's web site. In some instances, the manufacturer provides an alternative size, which is usually the next smallest length available, and the surgeon must decide which recommendation to use."

- *Khalifa YM, Moshirfar M, Mifflin MD, Kamae K, Mamalis N, and Werner L. "Cataract development associated with collagen copolymer posterior chamber phakic intraocular lenses : Clinicopathological correlation". Journal of Cataract and Refractive Surgery 2010; 36:1768-1774.*
- *Staar Surgical Co. Visian Phakic Intraocular Lens. Available at http://www.staarvision.com. Accessed June 11, 2010.*

Question for Panel Discussion

Based on all available data and the sizing method used in the clinical studies, do you believe that the directions for use concerning sizing are adequate to reasonably ensure predictable and safe postoperative vaulting?

Endothelial Cell Loss (ECL)

- TICL Study: ECL not assessed
- MICL PMA: % change endothelial cell density (ECD) from baseline to 3 yrs
- MICL PAS: Specular microscopy performed on a sub-group of eyes

ECL: MICL PMA

- % change ECD from baseline to 3 yrs = 8.9% (SD 8.5%)
- Available data from the clinical study indicated a continual steady loss of ECD of -2.2% per year
  - » In contrast, mean ECD loss/year in normal adults ranges from 0.22-0.60% in published literature*
- Contraindications in MICL labeling set minimum ECD criteria that should result in > 1000 cells/mm^2 at 75 yrs of age

*McCarey BE, Edelhauser HF, Lynn MJ. Review of corneal endothelial specular microscopy for FDA clinical trials of refractive procedures, surgical devices, and new intraocular drugs and solutions. Cornea. 2008 Jan;27(1):1-16.

McCarey BE. Noncontact specular microscopy: a macrophotography technique and some endothelial cell findings. Ophthalmology. 1979; 86:1848–60.

Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. Investigative Ophthalmology & Visual Science. 1997; 38:779–82.

ECL: MICL PAS #1

- Cumulative mean loss: 11.0% over ≥5 yrs
- Greater loss: 16 eyes with ECD ≤1500 or ≥30% reduction in ECD from preop*
  - » 4 eyes with traumatic loss from surgery (>30% ECL at first postop measure)
  - » 2 eyes met these criteria although no preop ECD measurement and no data >2 years postop
  - » 10/115 (8.7%) of eyes with ECD data at preop and ≥5 yrs postop had significant ECL (>30% loss from preop)†

** or earliest visit with ECD data available*

† *these eyes were not designated as "outliers" by any standard statistical methodology*

ECL: MDRs and Published Literature

- MDRs
  - » 1 case explanted due to ECL
    - Preop endothelial cell count (2009): 3,369 cells/mm
    - Postop endothelial cell count (2010): 1,089 cells/mm
  - » 30 MDRs mention corneal edema or decompensation

- Published Literature
  - » Mean ECL range 2-12%
    - Avg follow-up 30 months (range:12 – 48)

ECL after Cataract Surgery

Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology. 1994 Jun;101(6):1014-22; "Discussion by Alan Sugar, MD" 1022-3.

- Limitations identified by Dr. Sugar:
  - » Cataract extraction in 253 eyes from 1976 to 1982
    - Intracapsular via cryoextractions
    - Extracapsular via nuclear expression
  - » "…selected their own patients from the previous prospectively assigned groups for a 10-year analysis….By the 10-year follow-up visit, only 67 eyes (26.5%) in 57 patients were available for endothelial examination….Only seven patients had posterior chamber IOLs."
  - » "The current cell loss seen after posterior chamber phacoemulsification[1] and the use of viscoelastics[2] would be expected to raise the baseline on which exponential cell loss acts and further protects the cornea."

[1] Werblin TP. Long-term endothelial cell loss following phacoemulsification: model for evaluating endothelial damage after intraocular surgery. Refract Corneal Surg 1993; 9:29-35.
[2] Koch DD, Liu JF, Glasser DB, et al. A comparison of corneal endothelial changes after use of Healon or Viscoat during phacoemulsification. Am J Ophthalmol 1993; 115:188-201.

Question for Panel Discussion

Potential adverse events identified in the available clinical data pertaining to the TICL lens platform include:

- Inappropriate vault
- Cataract formation
- Secondary surgical interventions
- Endothelial cell loss (ECL)
- Glaucoma and narrowing of the angle

Given the available treatment alternatives for lower myopes, do you believe the safety profile of the TICL supports approval of the full range of spherical equivalent powers proposed for approval (-3D to -16D)?

Effectiveness
STAAR Surgical Visian Toric Implantable Collamer® Lens

Gene Hilmantel, O.D., M.S.
Clinical Reviewer
Division of Ophthalmic and Ear Nose and Throat Devices
Food and Drug Administration
Office of Device Evaluation

March 14, 2014

Factors Impacting Effectiveness of Toric IOLs*

- Accuracy of axis alignment
  - » ~ 3.3% reduction in astigmatism correction for each degree of misalignment
- Measurement accuracy of preop cylinder
- Accurate prediction of surgically induced astigmatism

** Discussed in:*

- *Rubenstein JC and Raciti M. Approaches to corneal astigmatism in cataract surgery Curr Opin Ophthalmol 2013, 24:30–34*
- *Visser N, et al. Vector Analysis of Corneal and Refractive Astigmatism Changes Following Toric Pseudophakic and Toric Phakic IOL Implantation. Invest Ophthalmol Vis Sci. 2012;53:1865–1873.*

Accuracy of Axis Alignment

CORRECT AXIS ORIENTATION

↓

REDUCE MANIFEST ASTIGMATISM

↓

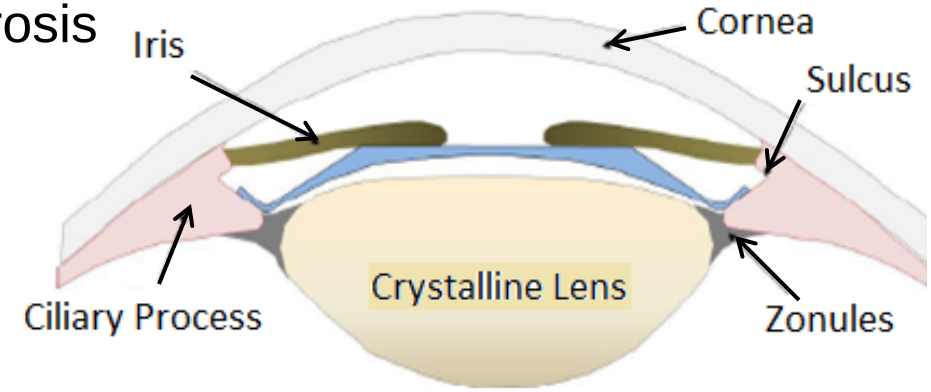
IMPROVED UNCORRECTED VISUAL ACUITY

↓

PATIENT SATISFACTION

Factors Influencing Accurate Axis Alignment

- Intraoperative:
  - » Difficulties in achieving correct orientation
- Postoperative:
  - » Rotation of lens
    - IOLs in the bag: capsular fibrosis may stabilize
    - ICL in the sulcus*: no fibrosis



**Applicant suggests that the ICL footplates "are designed to interact with the ridges and grooves on the surface of the ciliary process and provide more frictional stability"*

TICL Study "Effectiveness Parameters"

- Decrease in Refractive Cylinder & Myopia ("primary efficacy variable")
- Predictability of cylinder and sphere (intended correction vs.. achieved correction)
  - » ≥75% achieve MRSE* within 1.00 D of intended
  - » ≥ 50% achieve MRSE* within 0.50 D of intended
  - » ≥ 65% achieve cylinder within 1.00 D of intended
  - » ≥ 40% achieve cylinder within 0.50 D of intended
- Refractive stability (i.e., change in manifest sphere and cylindrical outcomes over time)

*MRSE = manifest refraction spherical equivalent

TICL Study
"Effectiveness Parameters" (cont'd)

- Improvement in Uncorrected Visual Acuity (UCVA)
  - 85% of eyes should achieve an UCVA of 20/40 or better (for eyes with BSCVA ≥20/20 preop)
- Patient Satisfaction (subjective evaluation)
- Rotation of the ICL

ANSI Toric Standard Recommendations vs. Toric ICL Study

	ANSI Z80.30 (2010): Toric (modification of phakic IOL)	TICL Study
Main Effectiveness Outcomes	• Percent Reduction of Manifest Cylinder (Achieved / Attempted)	• Reduction of Manifest
		• Predictability
		• Improvement of Acuity
	• Lens Axis Misalignment • Rotational Stability	• "Rotation of ICL" *Misalignment and stability analyzed*
Method: Axial Misalignment	• Precision: Detect 5° shift (e.g., image capture) • Should Account for head tilt	• Visual "Clock Hours" *Precision not known*

TICL Effectiveness Outcomes

Decrease in Refractive Cylinder & Myopia*

- **Refractive Cylinder**
  - » Preop Mean (SD): 1.95 (0.85) D
  - » 12 Month Mean (SD): 0.52 (0.48) D
    - Mean Change: -1.43 D ($p < 0.001$)
- **MRSE**
  - » Preop Mean (SD): -9.38 (2.67) D
  - » 12 Month Mean (SD): +0.03 (0.46) D
    - Mean Change: 9.41 D

* 194 eyes with preop and ≥12 month data

Decrease in Cylinder: Percent Reduction of Cylinder* Stratified by Preop Cyl

Preop Manifest Cylinder†	N	Percent Reduction of Cylinder at ≥ 12 Months*	
		Mean % (spectacle pl)	Mean % (corneal pl)
All	194	78	71
1.0	39	75	66
>1.0 to 2.0	86	71	63
>2.0 to 3.0	45	87	84
>3.0 to 4.0	24	88	84

* (Achieved reduction)/(Attempted reduction)

† measured in the spectacle plane

Decrease in Cylinder: Surgically Induced Astigmatism (SIA)*

- The STAAR calculator assumes 0 D SIA
- Study Results*:
  - » Mean SIA magnitude: 0.66 D (a component is the imprecision of keratometry measurements)
  - » Vector “Spatial Median”: 0.2 D (with the rule)
- FDA-Requested Analysis: Vectorially add change in keratometry to preop manifest cyl (for each eye)
  - » For most ICL cylinder powers SIA would cause mean increase in refractive cylinder

*189 eyes with ≥12 month keratometry

Predictability of Refractive Cylinder and MRSE*

- **Refractive Cylinder**
  - » Within ± 1.00 D of attempted: 92% (179/194)
    [protocol target was ≥ 65%]
  - » Within ± 0.50 D of attempted: 70% (135/194)
    [protocol target was ≥ 40%]
- **MRSE**
  - » Within ± 1.00 D of attempted: 97% (189/194)
    [protocol target was ≥ 75%]
  - » Within ± 0.50 D of attempted: 77% (149/194)
    [protocol target was ≥ 50%]

*194 eyes with preop and ≥12 month data

Stability of Manifest Refraction: Cylinder Magnitude Changes*

	1 – 3 Months	3 – 6 Months	6 – ≥ 12 Months
% of eyes w/ change			
≤ 1.00 D	98%	99%	98%
≤ 0.50 D	84%	89%	85%
Mean Change	0.00D	-0.03D	0.04D
N	184	172	177

*Analysis of paired adjacent visits; cylinder in corneal plane

Stability of Manifest Refraction: Cylinder Vector Changes*

	1 – 3 Months	3 – 6 Months	6 – ≥ 12 Months
% of eyes w/ change			
≤ 1.00 D	97%	97%	97%
≤ 0.50 D	78%	84%	80%
Mean Change	0.26D	0.23D	0.26D
N	184	172	177

*Analysis of paired adjacent visits; cylinder in corneal plane

Improvement in Uncorrected Visual Acuity: % of Eyes with UCVA ≥ 20/40

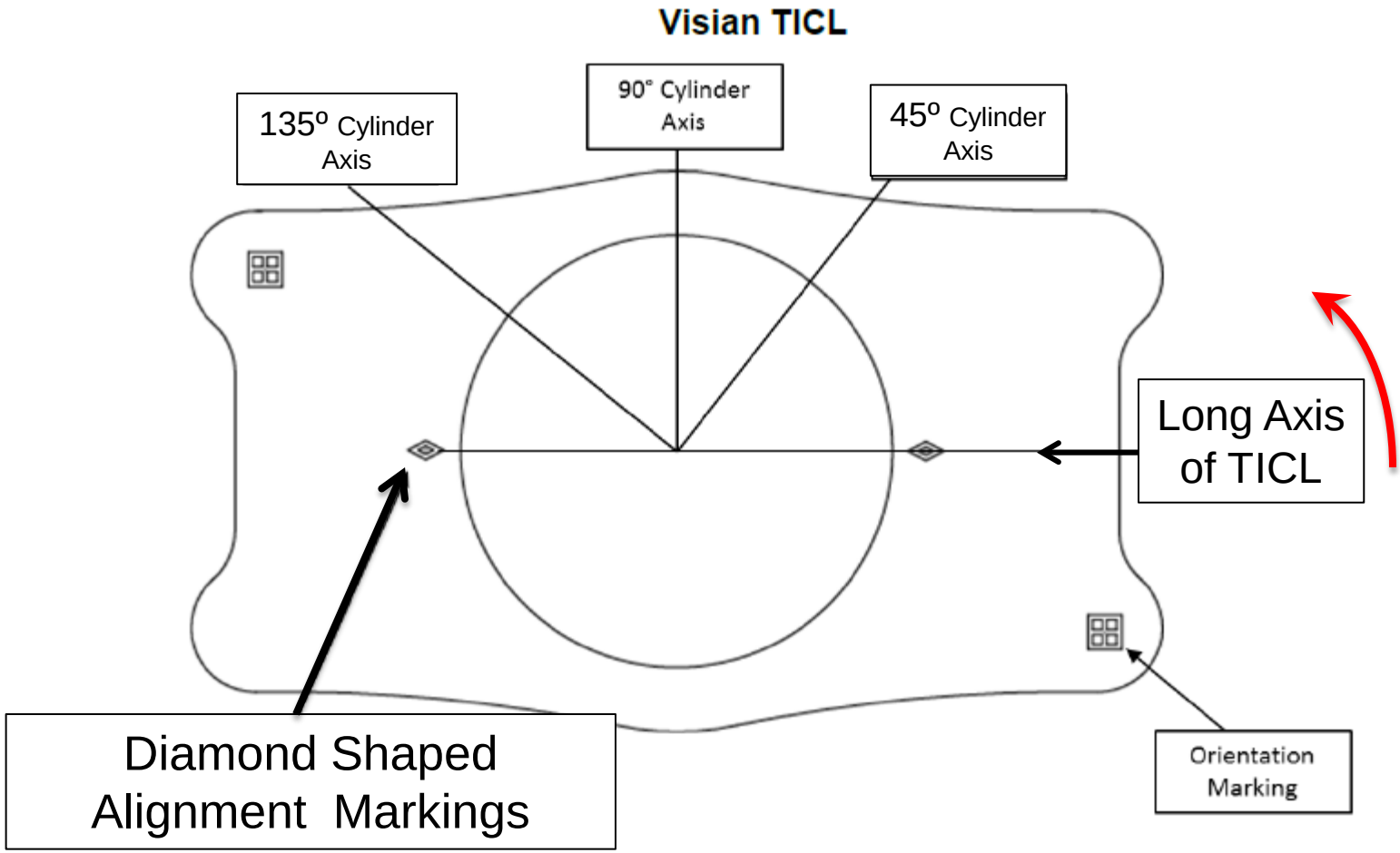
- Preop: 0% (0/210)
- ≥ 12 Months
  - » In eyes with preop BSCVA ≥ 20/20: 100% (159/159)
    [protocol target was ≥ 85%]
  - » All available eyes: 95% (184/193)

Patient Satisfaction*

- Assessed using non-validated questionnaire
- Results
  - » Satisfaction with surgery
    - 87% (180/207) were “extremely” or “very” satisfied
    - 2% (4/207) were “fairly” satisfied
    - 0% (0/207) were “moderately” or “unsatisfied”
    - 11% (23/207) were unreported or missed visit
  - » Willing to have the surgery again
    - Yes: 87% (181/207)
    - No: 1% (2/207)
    - Undecided: 0.5% (1/207)
    - Unreported: 11% (23/207)

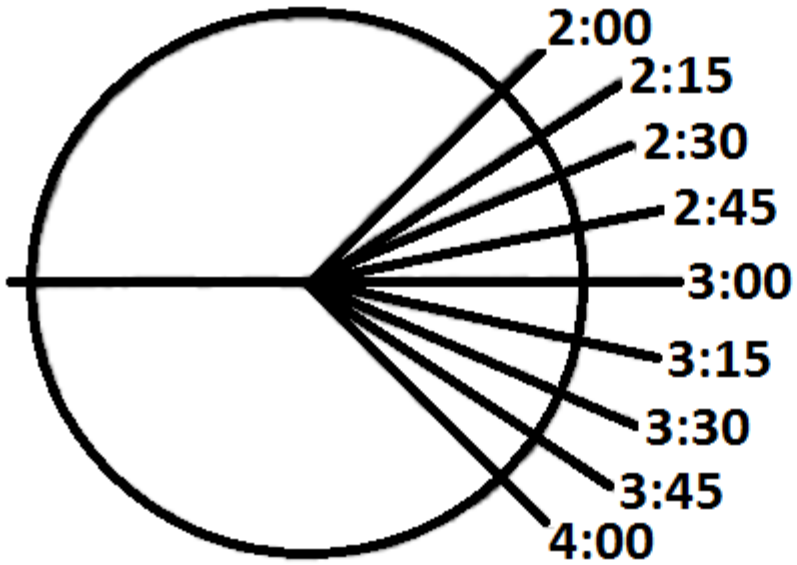
* at ≥ 12 months

Rotational Misalignment: Direct Measurement Methodology



Rotational Misalignment: Direct Measurement Methodology (cont'd)

- Case Report Form: Orientation of Lens



Other (specify) _____

- Significant variability in reporting
- No standard operating procedure (SOP) in method of assessment

Rotational Misalignment: Direct Measurement – Background

- Original Toric ICL Submission
  - » Analysis of 13 eyes with >15º TICL rotation between visits
  - » Applicant stated that it appeared that there were significant errors in some rotational misalignment measurements
    - Based upon inconsistency with refractive cylinder data
- In Response to FDA-Requested Clarification, Applicant:
  - » Audited eyes with significant rotation or misalignment
  - » Modified several analyses and some data
  - » Acknowledged that “clock hours” methodology was, “clearly a very gross approximation and subject to considerable opportunity for error”

Rotational Misalignment: Direct Measurement – Background

- FDA requested further clarification of some contradictory analyses --
  - » FDA offered alternative to:

    "…rely primarily upon the refractive data for information concerning axis position (if the direct axial measurement method was too gross to be very useful)."
  - » Applicant agreed to this alternative, acknowledging limitations of the direct measurement method used
- FDA suggested additional analyses of rotational misalignment calculated through vector analysis of the manifest cylinder results

Rotational Misalignment: Background

- For Completeness, Rotational Misalignment Analyses are Presented from 2 Methodologies:
  - » Direct Measurement†
  - » "Error of Angle"* (EA) -- the angular difference between the achieved treatment and the intended treatment (calculated from manifest cylinder)

† Note that some direct measurement data changed significantly after the data audit; eliminating some of the errors in earlier submissions

** Eydelman MB, et al. Standardized Analyses of Correction of Astigmatism by laser systems that reshape the cornea. J Refract Surg.2006;22:81-95.*

Results for Rotational Misalignment: Direct Measurement

Misalignment From Intended	% of eyes		
	3 Mos	6 Mos	≥ 12 Mos
< 10°	88%	88%	87%
< 20°	98%	99%	96%
< 30°	100%	100%	99%
N	**184**	**145**	**187**

- Intra-op: 9 TICLs placed at ≥15º from intended
- Post-op: 2 eyes had early SSIs greatly reducing large misalignment

Results for Rotational Misalignment: Direct Measurement (Stability between visits)

- Percent of eyes with ≤ 5º rotation:
  - » 1 day - 1 week: 98% (118/121)
  - » 1 week - 1 month: 96% (148/155)
  - » 1- 3 months: 95% (141/148)
  - » 3 - 6 months: 98% (133/136)
  - » 6 - ≥12 months: 94% (132/140)

Rotational Misalignment: Direct Measurement – Additional

- Above analyses include 123 instances of eyes seen outside of protocol visit windows, including:
  - » 3 month visit: 34 eyes
  - » 6 month visit: 15 eyes
  - » 12 month visit: 48 eyes
  - » Created inconsistent time spans for stability analyses

Rotational Misalignment: Direct Measurement – Additional (cont'd)

- Missing Data
  - » Total: 280/1249 (22%) of potential postop rotational orientation observations
    - 213 observations not made, but patient present
    - 67 missing because subject missed visit
  - » Operative visit: 4/210 (2%)
  - » 1 day visit: 82/210 (39%)
  - » 6 month visit: 62/207 (30%)
  - » ≥12 months: 20/207 (11%)

Results for Rotational Misalignment: Vector EA Analysis from Manifest

Error of Angle	Percent of Eyes at ≥ 12 Months	n/N
< 10º	70%	135/194
< 20º	90%	174/194
< 30º	97%	188/194

6 eyes with EA > 30º at ≥ 12 months

Results for Rotational Misalignment: Vector EA Analysis from Manifest (Stability between visits)

- Percent of eyes that showed ≤ 5º of axial rotation:
  - » 1 week - 1 month: 77% (148/193)
  - » 1 month - 3 mos: 75% (137/184)
  - » 3 mos – 6 mos: 79% (135/172)
  - » 6 mos – 12 mos: 78% (138/178)
- Percent of eyes showing >15º rotation at

  6 mos – 12 mos: 9% (16/178)

Limitations of Vector EA Analysis for Rotational Misalignment

- Absence of standard operating procedure for refraction
- For low residual manifest cylinder - Substantial imprecision
- For small levels of TICL cylinder correction – “Error of Angle” analysis can have high numbers of false negatives and false positives in detecting axial rotation
  - » 47% of eyes (98/210) were implanted with ICL cyl power < 1.6 D (~1.2 D in the corneal plane)

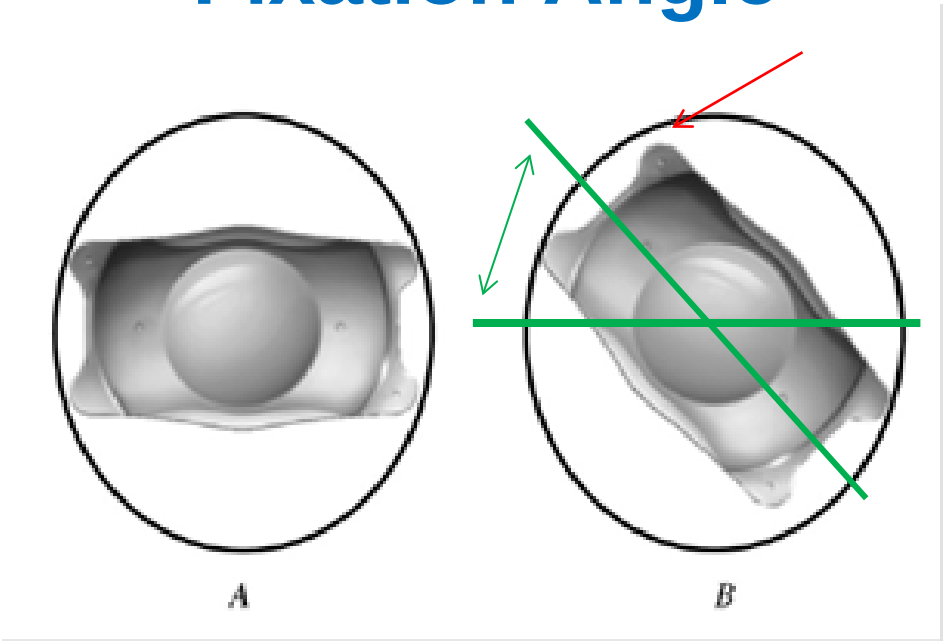
Question for Panel Discussion

Rotational misalignment and axial stability were assessed by direct observation and manifest refraction. In light of the following:

- Limitations of each method
- Missing data (22% of all postop direct measurements)
- “Out-of-window” visits (123)

Do the rotational misalignment and manifest refraction data provide reasonable assurance that the TICL can achieve desired axial orientation and rotational stability?

Fixation Angle



- Angular amount of surgical rotation from horizontal
- In most eyes, ciliary sulcus has a vertical oval shape
  - » Theoretical concern: Rotation might cause “footplate to become loose”

Figure from Mori T, et al. J Cataract Refract Surg 2012; 38:568–573

Fixation Angle (cont'd)

- Small but significant correlation ($r^2 = 0.114$, $p = 0.01$) between intraoperative fixation angle and postoperative TICL rotation*
  - » Eyes with fixation angles greater than 5 degrees were 5.6 times as likely to have postoperative rotation as eyes with smaller fixation angles

**Mori T, et al. J Cataract Refract Surg 2012; 38:568–573*

Fixation Angle TICL Study*

Postoperative Rotation Stratified by Fixation Angle

Fixation Angle (degrees)	N	Mean EA from Manifest	Mean Rotational Misalignment (Direct Measurement)
0	11	7.7º	4.6º
1 - 5	72	8.9º	4.0º
6 - 10	49	8.2º	5.1º
11 - 15	28	6.9º	4.9º
16 - 22	**33**	**10.4º**	**6.8º**
> 22**	1	0.7º	0.0º

* 194 eyes at ≥12 months

** 1 eye had a 90 degree fixation angle; noted as a protocol deviation

Question for Panel Discussion

Fixation angle is the amount of intraoperative surgical rotation used to achieve the desired TICL axial orientation. 17% of eyes (33/210) in the Visian TICL study had a fixation angle >15°. Some published literature indicates that large fixation angles may be associated with greater postoperative rotation. Is there sufficient information available to support directions for use with fixations up to 22.5º, as in the proposed labeling?

Post-Approval Study (PAS) Considerations

Youlin Qi, M.D., M.P.H.

Division of Epidemiology
Office of Surveillance and Biometrics

March14, 2014

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

Important Postmarket Issues

1. Progressive endothelial cell density (ECD) loss;
2. Possibility of late cataract development and the association with vault change;
3. Stability of the corrected cylinder axis over time;
4. Visual disturbances after TICL implantation.

Applicant's Proposed PAS

Study Design	• Single arm, prospective, multicenter clinical study • Enrollment of 150 patients (up to 300 treated eyes) from 5 to 10 centers in the United States
Hypothesis Tested Study Endpoints	1. Endothelial cell density over 5 years • Minimum of 100 eyes • Followed at day 1, week 1, months 1, 3, 6, 12, 24, 36, 48, 60 • Maximum mean loss of 18% at 5 years 2. Incidence of cataract development over 5 years • Minimum of 100 eyes • Followed at day 1, week 1, months 1, 3, 6, 12, 24, 36, 48, 60 • Maximum rate of 4% at 5 years 3. Rotational stability over 1 year • Minimum of 61 eyes • Followed at months 1, 3, 6, 12 • Minimum of 90% of eyes rotate ≤ 5°

Applicant's Proposed PAS (cont'd)

Descriptive Study Endpoints	4. UCVA, BSCVA, decrease in myopia and cylinder on higher (3.50D and 4.00D) astigmatism groups over 1 year • Minimum of 61 eyes • Followed at week 1, months 1, 3, 6, 12 5. Visual Disturbances evaluated by questionnaire over 1 year • Minimum of 61 eyes • Followed at months 6 and 12

FDA Assessment of PAS

- Additional safety endpoints of concern;
- Mean ECD loss versus proportion of eyes with large ECD loss, and need for concurrent control group;
- Length of follow-up for long term cataract formation may not be sufficient;
- Questionnaire for visual disturbances not specified.

Questions for Panel Discussion

a) The TICL study did not assess ECD loss. The MICL PAS demonstrated a mean ECD loss of 11% at 5 years. However, 6% of eyes (10/159) had ECD loss greater than 30%. The significance of this result is difficult to interpret due to the lack of an active control arm. In light of this please discuss whether the TICL PAS should:

   i. include an active control arm?

   ii. be powered to detect significant differences in the proportion of eyes with large changes (e.g., >30 % loss from baseline)?

b) Please discuss the adequacy of the endpoints in the PAS, and if there are any additional endpoints or considerations that need to be addressed in the PAS.

c) Please discuss the appropriate duration of follow-up in order to assess safety performance of the device, with specific consideration for late cataract formation in the postmarket setting.